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ON THE NATURE OF TUMOR-HOST IMMUNOLOGICAL RELATIONSHIPS

V. S. Erkhov and A. I. Ageenko

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TRANSLATED BY THE RALPH MCELROY TRANSLATION COMPANY

ON THE NATURE OF TUMOR-HOST IMMUNOLOGICAL RELATIONSHIPS

[K voprosu o prirode immunologicheskikh vsaimootnoshenii opukhol'-organizm]

Solving the problem of the nature of tumor-immunity relationships essentially means defining these phenomena as biological categories. There is a single logical path for defining phenomena of biological systems as biological categories – analysis of their evolutionary participation in perfecting the generation of biological variety. Until a phenomenon has been defined as a biological category, its boundaries are indistinct and its relationships to other phenomena of biological systems undefined.

The problem of immunity-tumor formation relationships is usually interpreted by using the terminologically narrow sense of "immunity" as "defense." This approach was most completely reflected in the notion of F. M. Burnet [9] concerning the role of immunological surveillance in tumor formation. The historically early approach of F. M. Burnet obviously corresponds to the viewpoint that immunity-tumor relationships have an unambiguous, unidirectional character of defense. "Defense" against what, strictly speaking? According to the ideas of F. M. Burnet, immunity arose in evolution as a method of "defense" against a tumor, since tumor formation leads to a decrease in the generation of biological variety. It should be stressed that in this way the main thing in the conception of this author is analysis of immunity-tumor relationship with respect to the main content of biological evolution – improving the method of generation of biological variety. Therefore, in his opinion, it is not immunity and tumor formation that are competing, but rather two methods of *generating variety*. It seems to us that the error of reducing tumor-immunity relationships to "defense" lies in identifying the method of generating variety with the phenomenonology of variety itself.

It is absolutely clear that the *method* of generating variety can be indivisible, but variety itself can at the phenotypic level have different selective potencies (can enter into competition), a partial expression of which may be antitumor surveillance. Therefore, if, phenomenonologically speaking, immunity carries out the function of surveillance of tumor formation, this does not in and of itself mean that immunity and oncogenesis utilize different methods of generating variety, i.e., that they have different regulatory foundations with regard to this trait.

At the same time, there is also doubt concerning the thesis that follows from the conception of F. M. Burnet that immunity arose in evolution as a system functioning by the principle of a system with negative feedback. As soon as the surveillance function of immunity possibly is merely a partial function of immunity, it is proper to cast doubt on the assertion that "self-other" discrimination is a basic function of immunity. If one adopts this hypothesis, it is logical to conclude that the system of immunological recognition evolved not by a path of

improving "self-other" discrimination, but rather by method of identifying and fixing in evolution the "self." Immunological recognition realized its potential polymorphism owing to mechanisms of self-recognition, i.e., involving mechanisms of positive feedback. In spite of the fact that extensive data giving evidence that immunogenesis includes recognition of "self" has been gained up to now (this was reflected in the network conception of N. K. Jerne [10]), in the "dual recognition" hypothesis of J. Sprent [13] and others, the facts in and of themselves cannot serve as proof that the system of immunological recognition arose in evolution as a system with positive feedback. The general considerations given above and the available experimental data that immunity involves obligatory inclusion of recognition of "self" into the process makes this hypothesis merely very likely. This uncertainty can to a substantial degree be reduced only if there is success in establishing that immunological mechanisms of self-recognition are included in the process of generating variety. Analysis of the immunity-tumor relationships can prove fruitful in solving this problem, since there is the possibility that basic changes of the parameters of immunity during oncogenesis have the same mechanism that supports generation of a variety of traits in the tumor system itself.

In the context of what has been said about the possibility of the appearance of immunological recognition in evolution as a system with positive feedback one cannot fail to mention the numerous facts pointing to structure-functional homology of receptive molecules of the system of immunological recognition, and of the convincing proof of the existence of a family of immunoglobulin genes [11], which points to the preexistence of a single ancestral gene. Thus, there is the possibility that immunity and tumor formation in a basic trait – the method of generating biological variety – have a common mechanism, that this mechanism functions as a system with positive feedback. At the same time, it can be concluded that proof of such a mechanism in a tumor will make the assertion of this same mechanism being included in the process of expanding the range of immunological recognition very probable.

It is clear that if a mechanism of generating a variety of traits functions in tumors as a system with positive feedback, then evolutionarily conservative traits of the tumor system that are obligatory for the tumor and stable in tumor progression must be included in this process. Embryonic tumor-associated surface differentiation antigens meet all of these requirements.

In evaluating the methodology of the traditional approach to determining the role of immunity in tumor formation (surveillance, control of cytodifferentiation, etc.). We consider the relationship of the categories of controlled and control to be *central*. In a purely verbal expression, for example: "immunological surveillance of tumor growth," "immunity as control of cytodifferentiation," and so forth, the functions of immunity and what is controlled by it are, as it were, scattered "to different sides of the barricades." Meanwhile such a state of affairs hardly corresponds to reality. Here we have in mind that in self-developing systems the level of

complexity (principles of organization) of control and what is controlled out of necessity must be indivisible if only because in the final account a self-organizing system includes the complexity of its own control as its own property. According to the traditional view of the role of immunity, it includes a function only of negative control. It seems to us that this underestimates the circumstance that immunity is a system having extreme polymorphism (this system discriminates approximately 10^6 antigens [9]). It is difficult to imagine that the diversity of "export" (a system with negative feedback) would exceed in its complexity the general technological level of the system. In a specific expression, the organization of immunity and, as a minimum, the genetically predetermined [9] plurality of receptors of immunological recognition, according to the network theory of N. K. Jerne [10], also corresponds to a predetermined plurality of idiotypic determinants. The sense of our arguments comes down to the fact that the method of generating variety that is inherent to immunity understood in the narrow sense becomes its attribute at a certain level of ontogenesis. I would also like to give a few final thoughts on the methodology of determining immunity as control (no matter what of). In our opinion such directions are internally contradictory, since immunity itself is cytodifferentiation (however, it evidently does not require additional control) and, at the same time, the main if not the only function of immunity is control of cytodifferentiation. It is not surprising that chains of "control of controls" can be continued to infinity.

As follows from what has been said, if one doubts the function of immunological recognition only as control (of tumor growth or of cytodifferentiation) in evolution and oncogenesis, then it is quite proper to suggest that immunological recognition arose and became fixed in evolution as a system with positive feedback, i.e., the generation of immunological recognition includes not only the function of immunity in the terminologically narrow sense, but it also necessarily includes the ability to recognize evolutionarily conservative structures.

In this connection one is struck by the fact that, in spite of the intensity of progressive selection acting in tumors, embryospecific surface antigens associated with tumor growth are evolutionarily conservative and stable in tumor progression [8]. It is logical to suggest that stabilizing selection in the tumor includes immunological recognition of its own embryonic surface antigens expressed in the tumor.

We have established that in tumors of varying etiology and histogenesis there functions a mechanism of immunological recognition of their own embryonic surface antigens [1-7]. It has been shown that contact of surface tumor cells and (or) cells of syngeneic embryos causes stimulation of the synthesis of DNA in tumor cells (stimulation is not dependent on the presence of growth factors); this phenomenon occurs in a serum-free medium and is blocked by anti-idiotypic antibodies to the embryonic stage-specific antigens. Stage-specific embryonic surface antigens associated with tumor growth are evolutionarily conservative and stable in tumor

progression. It is possible that there is a connection between the stability of this trait in tumor progression and a mechanism of their immunological recognition expressed in the tumors (autooscillation process). It is interesting that CEA [carcinoembryonic antigen] is constructed according to the domain trait and has high homology with domains of immunoglobulins [12]. In this article we will not dwell either on the exceptional importance of aspects of the nature of stage-specific surface embryonic antigens that are immunologically recognized in tumors or on analysis of possible mechanisms of the functioning of this system [1,6]. We believe it important to stress that, as follows from our argument given in this article, the question of the nature of tumor-host immunological relationships is not bounded by the framework of "inhibition-stimulation" logic. The basis of tumor-host immunological relationships in our opinion is the interaction of a dynamic (generating variety) constantly progressing microsystem of immunity (tumor) and the changed macrosystem of immunity (host). Clearly from this standpoint oncogenesis is realized when there is a coincidence of conditions of a change of immune status (for example, induction of clones of lymphocytes committed to surface differentiation embryonic antigens) and the appearance of a self-maintaining system (tumor) of immunological recognition of these antigens.

Thus, in the process of oncogenesis evolutionarily conservative differentiation embryonic antigens play a dual role: they are targets of immunological intensification of the growth of the tumor (exogenous stimulus) and, at the same time, they trigger proliferative processes in the cells of the tumor that have receptors for them (autostimulus of proliferation). Possibly they are the substrate that supports a universal mechanism of immortalization of tumor cells [1, 6].

Beyond this, immunological surveillance is an actually existing system of self-control of the systems of generation of variety of traits (differentiation) that accomplishes its function not only at the level of control of the possibility of the appearance of systems with a phenotypically different type of immunological variety (tumor); there is the possibility that surveillance is accomplished with regard to the tumor formed, since the significant probability that the phenotypic variety of these two apparently relative autonomous systems can enter into competition.

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Cellular Vesicle Called "Exosome," Preparation and Use Thereof in Immune Stimulation

[Vésicule cellulaire dénommée "exosome," leur préparation et utilisation dans la stimulation d'une réponse immunitaire]

Laurence Zitvogel et al.

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